REMARKS

Reconsideration is requested. Claims 43 to 58 are pending.

The specification has been amended to include a recitation of the incorporated subject matter. That is, the information contained in U.S. Patent No. 6,040,169 (a copy of which is attached) is incorporated by reference, pursuant to MPEP §608.01(p). A copy of MPEP §608.01(p) is attached for the Examiner's convenience. Section A of MPEP §608.01(p) indicates that essential material may be incorporated by reference to a U.S. patent. The Examiner's reference to section B in making a similar rejection in Paper No. 21 (at page 2) is not understood as the referenced WO 92/13943 (PCT/GB92/00179) is not an application relied on for benefit. The specification now only incorporates by reference a granted U.S. patent which the undersigned respectfully submits is proper. The Examiner is requested to withdraw the objection to the specification recited on page 2 of Paper No. 23.

The amended claims find support at page 5 of the specification, under the heading "Detailed Description" as well as the working examples. No new matter has been added.

The Section 112, first paragraph, rejection of claims 43 to 50 and 52 to 57 is traversed. The Examiner is requested to consider the following in this regard.

The applicants respectfully submit the pending claims do not cover a "whole universe of mutants" as suggested by the Examiner at page 4 of Paper No. 23. Indeed, the class of mutants covered by the invention is clearly defined and is fully supported by the specification and the incorporated text of U.S. Patent No. 6,040,169. The examiner

has also identified other prior art references that describe the production of HSV-1 mutants having a similar modification in the γ34.5 gene, e.g. R3616 (see Market et al, Neurosurgery, vol. 34, No. 4, April 1993). Therefore, it is clear that a high level of skill already existed in the art at the time and that the ordinarily skilled person would have had no difficulty in producing the HSV-1 mutants required to practice the present invention. Indeed, the applicants are not claiming the mutants per se as they already acknowledge that such mutants were already known in the art. The present invention relates to a novel method which uses the known, or subsequently developed HSV-1 mutants, which exhibit the same properties. The inventors have provided this novel method for the treatment of cancers using a specific known class of HSV-1 mutants which at the filing date of the present application were thought not to have the properties required to allow this treatment to be successful.

With regard to the mode of administration, the examiner has already acknowledged (by lack of rejection of claim 51 under 35 U.S.C 112) that a method of treating a metastatic tumour or melanoma comprising administering mutant 1716 is enabled. This claim does not specify any particular mode of administration and therefore, it must be assumed that it is considered enabling for **any mode of administration**. The Examiner has further acknowledged (See, page 4 of the Office Action dated March 1, 2000 (Paper No. 21)) that a "method of treating a metastatic tumor which occurs in but does not originate from the CNS comprising intra tumoral or intracranial injection of HSV-1 wherein HSV-1 has a non-functional gamma 34.5 gene in the long repeat region, wherein HSV-1 infects the tumor cells of the tumor" is also

considered enabled. The Examiner is urged to appreciate that claim 43 recites a step of infecting the actual tumour cells of the tumour.

Although questioned in the applicants response to Paper No. 21, the applicants do not believe the Examiner has explained why a method relating to a particular HSV-1 mutant 1716 is enabled for any mode of administration, whereas an identical method relating to other HSV-1 mutants falling within the same defined class as 1716, is only considered enabled for intratumoral or intracranial injection. Clarification in this regard is again requested in the event the rejection is maintained.

As stated previously, all mutants covered by the present invention, by definition, have the same therapeutic properties. Therefore, if a method relating to one HSV-1 mutant is considered enabled, then the applicants' submit a method relating to an equivalent HSV-1 mutant as defined by the claims should also be considered enabled. Withdrawal of the Section 112, first paragraph, rejection of claims 43-50 and 52-57 is requested.

Attached is a copy of the deposit receipt for mutant 1716. The specification has been amended to include this information. The applicants further note that beyond the statements made on page 11 of the Amendment of July 3, 2000, in this regard, the deposit will be replaced if viable samples cannot be dispensed by the depository. Withdrawal of the Section 112, first paragraph, rejection of claims 51 and 58 is requested.

The Section 103 rejection of claims 43 to 58 over U.S. Patent No. 5,585,096 in view of Olofsson (Arch. Virol., 1993, 128:241-256), Davey (Neurosurgery, 1991, 28:8 to

14), WO 92/13943 and Markert (Neurosurgery, 1993, 32:597-603) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

A brief review of each of the cited art documents is provided as follows and their combination is discussed as it compares to the presently claimed invention. Consideration of the following and withdrawal of the rejection are requested.

Olofsson et al are concerned with antiviral nucleoside analogue 5-n-propyl-2' deoxyuridine (PdU). PdU induces a pattern of interference with late steps in formation of N-linked glycans resulting in increased availability of viral glycoproteins for neutralising antibodies. The analogues effectively inhibit HSV DNA synthesis. The antiviral activity is dependent on phosphorylation of PdU and BvdU by the HSV-1 specified thymidine kinase (Tk) which makes the inhibition of DNA synthesis selective for HSV-1 infected cells. The authors show that PdU can block the formation of the oligosaccarides in HSV-1 infected B16 mouse melanoma cells, where multi-branched oligosaccarides are believed to contribute to the high metastatic potential of this cell line.

Markert et al are concerned with malignant glioma. Glioma are the most common form of malignant brain tumour. The authors investigate the effects of HSV-1 mutant *dl*sptk on these gliomas; *dl*sptk is a mutant with decreased neurovirulence which has been shown to kill human glioma cells in culture and in animal models, However, the authors state that the mutant is limited in use because it causes fatal encephalitis at higher doses. Therefore, the authors tested other HSV-1 mutants, such as R3616, to see their effects as antiglioma agents. They report that the virus mutants were

successful in killing glioma cells. There is no teaching or suggestion within this paper that such virus mutants could be used in the treatment of a metastatic tumour that occurs in but does not originate from the CNS.

U.S. Patent No. 5,585,096 relates to a γ34.5 and ribonucleotide reductase deficient HSV-1 mutant and its use in treating brain tumours. The patent contains a large list of possible tumour types that may be treatable using this mutant and included in that list are melanoma cells. The working examples contained in the application all relate to the treatment of brain tumours. The ordinarily skilled person would therefore be taking a great leap of faith to believe that such mutants could be effective on non CNS tumour types given that all of the teaching is concerned with brain tumours.

Davey et al are concerned with treatment of brain metastases from malignant melanoma using radiosurgery. There is no suggestion or teaching to use any other form of treatment. The authors conclude that radiosurgery is the answer to local tumour control and support this conclusion with excellent results.

As previously noted in the record, in order for an invention to be obvious over the prior art, three basic criteria must be met:

1) There must be some suggestion or motivation, either in the cited references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

2) There must be a reasonable expectation of success - not to be confused with an obvious desire to succeed; and

3) The prior art reference must teach or suggest all of the claim limitations.

U.S. Patent No. 5,585, 096 concerns an HSV-1 mutant having similar properties to those of the present invention. There may also be a suggestion within this patent that the mutant may be used in the treatment of tumour cells other than brain tumour cells, although this suggestion is not supported by any evidence of success. Therefore, the Examiner may argue that the disclosure of '096 provides the motivation for the skilled person to modify the teaching contained in '096 or to combine its teaching with other references. The applicants respectfully submit however that without further evidence there would not have been an expectation of success, as would be required to support a *prima facie* case of obviousness.

That is, the second criteria requires that the skilled person must proceed with a reasonable expectation of success. In accordance with well established case law, obviousness does not require absolute predictability. However, at least some degree of predictability is required. It is submitted that the ordinarily skilled person would not have attempted the modification of the teaching of ' 096 or its combination with further documents, with an expectation of success/degree of predictability for the following reasons.

At the time the application was filed, it was believed that HSV-1 inhabits cells of the nervous system. Therefore, use of the virus or a mutant thereof on a primary tumour of the brain would have been in line with scientific thinking and the teaching available. However, '096 contains a suggestion that goes against the current thinking at the time and therefore would have required serious evidence in support before the ordinarily skilled person would have followed the suggestion with any expectation of success.

Further, the other references cited by the examiner do not, in any way, encourage the skilled person to follow this motivation. Olofsson et al is concerned with an antiviral agent and its use in the treatment of melanoma cells infected with HSV-1. The paper teaches the use of an agent that can inhibit HSV DNA synthesis and, as a consequence, can selectively inhibit DNA synthesis in HSV-1 infected cells. Thus, the paper is concerned with using an antiviral agent to selectively kill cells already infected with HSV. This is a completely different technology to that of the present invention and indeed to the disclosure of '096 and therefore, it is submitted that the ordinarily skilled person would not have combined the teaching of these two documents.

Markert et al is concern with the treatment of malignant glioma. Gliomas are the most common form of malignant brain tumour. Therefore, this paper supports the statement made above that the scientific thinking at the time was that HSV-1 mutants could be used to treatment tumours of the central nervous system only, as it was known that HSV-1 inhabits cells of the nervous system. There is no teaching whatsoever in this paper that would have suggested to the ordinarily skilled person that such treatment could be used in tumour cells other than those of the brain. Therefore, the teaching of this paper goes no further than that of '096 and indeed further shows that the ordinarily skilled person would not have modified the teaching of '096 with any expectation of success. To modify the teaching would have been a scientific leap into the dark with absolutely no degree of predictability, as required by the case law on obviousness.

Davey et al teaches the treatment of brain metastases from malignant melanoma using radiosurgery. There is no teaching of using any other form of treatment.

Therefore, the applicants are unsure as to why any ordinarily skilled person would have combined the teaching of this paper with any of those mentioned above. The examiner may have cited Davey to show that there was a desire to treat metastatic melanoma occurring in the brain. This is not disputed. However, there is no teaching contained within this paper suggesting any form of treatment other than radiotherapy. Indeed, the paper described the success of the treatment. Clarification is requested however in the event the rejection is maintained.

The applicants submit that the ordinarily skilled person would not have combined the teaching of Davey et al with any of the other documents as it relates to a completely different technical field and the combination suggested by the examiner could only have been made in hindsight using the disclosure of the present invention. The teaching or suggestion to make the combination of documents and the reasonable expectation of success must both be found in the prior art and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In summary, the applicants submit that all three criteria required to establish a lack of inventive step, or obviousness, have not been met. Motivation may well have been provided by '096 to modify its teaching or combine it with other teachings, but given the scientific thinking at the filing date of the present application (see above and also Markert et al) such modification would not have been attempted with any expectation of success.

Further, the mutant HSV-1 of the present invention is incapable of replicating in and lysing neurons. Wild type HSV is neurotropic and by definition preferentially infects

and lyses CNS neurons causing encephalitis. In an embodiment of the present invention, mutant 1716, has been shown incapable of doing this. Melanomas are derived from melanocytes which originate during embyogenesis from the neural crest - the same origin as adult neurons. As the mutant HSV-1 of the present invention cannot infect or replicate in neurons, it would seem likely that it would also not be able to replicate in melanoma cells given that the cells are derived from the same origin.

Thus, it was extremely unexpected and, by inference, totally unpredictable that the HSV-1 mutants of the present invention would be able to infect and lyse melanoma cells while lacking in neurovirulence.

In order for someone to attempt this with an expectation of success, they would have needed some encouraging evidence having been presented by the prior art. As none exists, it is submitted that an inventive step has taken place to arrive at the present invention and the Section 103 rejection should be withdrawn.

The Section 112, first paragraph, rejection of claims 43 to 58, as described in ¶8 of Paper No. 23, is traversed for the reasons noted above. Reconsideration and withdrawal of the rejection are requested.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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MARKED UP CLAIMS

43. (Amended) A method of treating a metastatic tumour which occurs in but does not originate from the central nervous system of a human which method comprises the step of administering to the said human an effective amount of a mutant herpes simplex virus type 1 which has a non-functional γ34.5 gene in the long repeat region R_L, said gene having been modified by deletion, insertion or substitution such that it does not express the normal product or a functionally equivalent product of said gene and wherein the mutant HSV-1 infects and replicates within the tumour cells of the tumour.

52. (Amended) A method of treating a melanoma cancer in a human which method comprises the step of administrating to the said human an effective amount of a mutant herpes simplex virus type 1 which has a non-functional γ34.5 gene in the long repeat region R_L, said gene having been modified by deletion, insertion or substitution such that it does not express the normal product or a functionally equivalent product of said gene and wherein the mutant HSV-1 infects and replicates within the tumour cells of the tumour.